IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PERNIX IRELAND PAIN DAC and PERNIX THERAPEUTICS, LLC,	)	
Plaintiffs,	)	
v.	)	C.A. No. 16-139-WCB
ALVOGEN MALTA OPERATIONS LTD.,	)	
Defendant.	)	

OPENING BRIEF IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT OF NO INVALIDITY UNDER 35 U.S.C. § 101

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I. Nature and Stage of Proceedings

Plaintiffs ("Pernix") sued Alvogen for infringement of patents that cover Pernix's Zohydro® ER.[1] Alvogen seeks to sell infringing generic copies of Zohydro® ER before the patents-in-suit expire.

On April 11, 2016, Alvogen (along with then co-Defendant Actavis, which has since been dismissed from the case pursuant to a settlement) filed a motion to dismiss under Fed. R. Civ. P. 12(b)(6), asserting the claims of the '760 patent are invalid because they recite ineligible subject matter under 35 U.S.C. § 101. D.I. 14. After Pernix filed an amended complaint asserting additional related patents (D.I. 22), Alvogen filed another motion to dismiss under § 101. D.I. 24. The Court has not ruled on Alvogen's motion, which Pernix opposed (D.I. 25).

The Court held a *Markman* hearing and then issued an order construing the disputed terms in the claims of the patents-in-suit, on August 3, 2017. D.I. 69. Expert discovery closed on February 27, 2018. Pernix now moves for summary judgment that the asserted claims are not invalid under § 101.

II. Summary of Argument

The Court should grant summary judgment because the claims of the patents-in-suit recite eligible subject matter under § 101.

1. First, the claims are not directed to natural phenomena but rather to a method of altering a natural condition (pain) by treating it with a non-naturally occurring oral dosage unit comprising an extended release formulation of a semi-synthetic opioid.

[1] Pernix dropped patents and claims to narrow the issues in the case, and currently asserts claims 1-4, 11-12, 17 and 19 of U.S. Patent Nos. 9,265,760 ("the '760 Patent"), and claim 1 of U.S. Patent No. 9,339,499 ("the '499 Patent") (collectively, the "asserted claims" of the "patents-in-suit."). The patents-in-suit share a common specification.

2. Second, the claims do not recite a conventional method, as this Court already determined when it construed the claims and held that "the [claimed] method of treating pain in the hepatically impaired patient is ***different than the prior art's method*** of treating pain in that same patient." D.I. 69 at 3 n.2 (emphasis added).

3. Finally, Pernix's patents do not raise preemption concerns because the claims are confined to specific methods of treating pain using certain hydrocodone oral dosage units that produce a particular pharmacokinetic profile and do not require an adjustment in the starting dose when administered to patients with mild and moderate hepatic impairment relative to patients without hepatic impairment.

III. Facts

Pain is the most common reason for doctor visits in the United States. Ex. A, '760 Patent col. 1:33-37.[2] It can be acute, lasting until the underlying condition is healed or removed, or chronic, persisting for years. *Id.* Physicians prescribe Pernix's Zohydro® ER, an extended release ("ER") formulation containing hydrocodone (an opioid), to manage pain severe enough to require daily, around-the-clock, long-term treatment for which alternative treatment options are inadequate. *Id.* at 1:48. Hepatic impairment (*i.e.*, reduced liver function) complicates treatment of pain because the liver metabolizes (breaks down) most opioids. So the same dose of an opioid generally leads to higher blood levels of drug (C_{max} and AUC) in hepatically impaired patients compared to patients without hepatic impairment,[3] meaning that hepatically impaired patients receive too much drug (*i.e.*, an overdose), which can cause sedation, respiratory

[2] Unless otherwise indicated, "Ex." refers to an exhibit attached to the Declaration of Josh Calabro, Esq.

[3] C_{max} and AUC are pharmacokinetic ("PK") parameters that measure how well and quickly the body breaks down a drug. C_{max} refers to the maximum concentration of drug in the patient's blood, and AUC (Area Under the Curve) is a measure of total exposure to the drug over time. *Id.* at 11:12-23.

depression, or death. *Id.* at 2:44-47. Thus, physicians ***decrease*** the starting dose of opioids in patients with hepatic impairment to counter the effect of reduced liver function. *Id.* at 2:52-56. Doing so, however, complicates treatment. Unable to rely on the starting dose known to provide safe and effective pain relief in the normal patient population, physicians instead must monitor each hepatically impaired patient individually while adjusting dosages to try to safely achieve efficacy on a case-by-case basis.

ER formulations like Zohydro® ER release their active ingredient over a longer time compared to immediate release ("IR") formulations. The patents-in-suit describe five prior art commercial ER opioids that required dosage adjustments when administered to hepatically impaired patients. *Id.* at 3:10-4:29. Additionally, the patents-in-suit discuss the 2013 Bond Abstract with data on another hydrocodone ER formulation. That product, which was later approved by the FDA as Teva's Vantrela™ ER, had a clinically significant difference in AUC in patients with moderate hepatic impairment. In particular, "the delivery of ***[ER] hydrocodone*** . . . led to ***systemic exposure to hydrocodone*** [AUC] ***that was ~70% higher in subjects with moderate hepatic impairment vs normal hepatic function***." *Id.* at 2:56-65. Such increases in AUC or C_{max} "can lead to many problems, including need for adjusting dose, complications for physicians in prescribing, need for liver function tests, lack of availability of correct doses, lack of availability of certain medications to those with hepatic impairment, and overdosing." *Id.* at 4:30-36. The increase in AUC seen with the Vantrela™ ER hydrocodone product required a label instruction stating that patients with mild or moderate hepatic impairment should "[i]nitiate therapy with ***one half of the recommended initial dose*** and titrate carefully." Ex. B at 1 (emphasis added).

The inventors of the patents-in-suit unexpectedly found that physicians could prescribe the ***same*** starting dose of certain hydrocodone ER compositions in patients with and without hepatic impairment, thus providing a safer and simpler way of treating those patients. Ex. A at 4:40-65. Administration of those ER compositions minimizes the increase in AUC and C_{max} that one normally expects in hepatically impaired patients, rendering that increase "not clinically significant." *Id.* at 5:37-41, 23:27-38.

The asserted claims recite methods of treating pain in a patient with mild or moderate hepatic impairment by administering an ER hydrocodone oral dosage unit. The claims require particular PK profiles for patients with mild and moderate hepatic impairment, and/or require no adjustment in the starting dose for patients with mild and moderate hepatic impairment relative to patients without hepatic impairment.

Independent claim 1 of the '760 patent recites:

> 1. A method of treating pain in a patient having mild or moderate hepatic impairment, the method comprising:
>
> administering to the patient having mild or moderate hepatic impairment a starting dose of an oral dosage unit having hydrocodone bitartrate as the only active ingredient,
>
> wherein the dosage unit comprises an extended release formulation of hydrocodone bitartrate, and
>
> wherein the starting dose is not adjusted relative to a patient without hepatic impairment.

Asserted claims 2-4 and 11 depend from claim 1 and add limitations concerning the AUC and C_{max} profiles. Independent claim 12 of the '760 patent recites:

> 12. A method of treating pain in a patient having mild or moderate hepatic impairment, the method comprising:
>
> administering to the patient having mild or moderate hepatic impairment an oral dosage unit having hydrocodone bitartrate as

> the only active ingredient, wherein the dosage unit comprises an extended release formulation of hydrocodone bitartrate,
>
> wherein the dosage unit provides a release profile of hydrocodone that:
>
> (1) does not increase average hydrocodone $AUC_{0\text{-}inf}$ in subjects suffering from mild hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 14%;
>
> (2) does not increase average hydrocodone $AUC_{0\text{-}inf}$ in subjects suffering from moderate hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 30%;
>
> (3) does not increase average hydrocodone C_{max} in subjects suffering from mild hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 9%; and
>
> (4) does not increase average hydrocodone C_{max} in subjects suffering from moderate hepatic impairment relative to subjects not suffering from renal or hepatic impairment in an amount of more than 14%.

Asserted claims 17 and 19 depend from claim 12 and have additional limitations concerning PK parameters. Independent claim 1 of the '499 Patent likewise claims a method of treating pain in hepatically impaired patients, and contains limitations concerning the maximum AUC difference between hepatically impaired patients and patients without hepatic impairment. Ex. C, claim 1.

IV. Argument

A. Legal Standard

1. Patent-Eligible Subject Matter

Section 101 provides that a patent may be obtained for "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof," excepting only laws of nature, natural phenomena, and abstract ideas from those broad categories of patent-eligible subject matter. *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347, 2354

(2014), quoting *Ass'n for Molecular Pathol. v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2116 (2013).

To prevail on their defense under § 101, Defendants must prove by clear and convincing evidence that: (1) the claims of the patents-in-suit are directed to a law of nature or a natural phenomenon, and, if so, (2) the additional elements of the claims lack an "inventive concept" that "transform[s] the nature of the claim into a patent-eligible application." *Mayo Collab. Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1296-97 (2012); *Alice*, 134 S. Ct. at 2355; *Ultramercial, Inc. v. Hulu, LLC*, 722 F.3d 1335, 1342 (Fed. Cir. 2013) ("[A]ny attack on an issued patent based on a challenge to the eligibility of the subject matter must be proven by clear and convincing evidence."), *cert. granted, judgment vacated sub nom., WildTangent, Inc. v. Ultramercial, LLC*, 134 S. Ct. 2870 (2014).

The Supreme Court has cautioned that courts must "tread carefully in construing [the subject matter eligibility] exclusionary principle lest it swallow all of patent law" because "[a]t some level, 'all inventions . . . embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas.'" *Alice*, 134 S. Ct. at 2354, quoting *Mayo*, 132 S. Ct. at 1293-94. Thus, "a process is not unpatentable simply because it contains a law of nature," and "an application of a law of nature . . . to a known structure or process may well be deserving of patent protection." *Mayo*, 132 S. Ct. at 1293-94 (citation omitted). "The 'directed to' inquiry [*i.e.*, *Alice* step one], therefore, cannot simply ask whether the claims ***involve*** a patent-ineligible concept, because essentially every routinely patent-eligible claim involving physical products and actions ***involves*** a law of nature and/or natural phenomenon." *Enfish, LLC v. Microsoft Corp.*, 822 F.3d 1327, 1335 (Fed. Cir. 2016) (emphasis original). Rather, the Court should consider "whether the claims . . . focus on a specific means or method . . . or are instead directed

to a result or effect that itself is the [ineligible concept] and merely invoke generic processes . . . ." *McRO, Inc. v. Bandai Namco Games Am., Inc*., 837 F.3d 1299, 1314 (Fed. Cir. 2016). *Alice* step two requires analysis of the claims as a whole, considering their "elements both individually and as an ordered combination," to determine whether they "recite well-understood, routine, conventional activity already engaged in by the scientific community." *Rapid Lit. Mgt. Ltd. v. CellzDirect, Inc*., 827 F.3d 1042, 1047 (Fed. Cir. 2016) (citation omitted); *accord Exergen Corp. v. KAZ USA, Inc.*, Case Nos. 2016-2315, 2016-2341, slip op. at 7-12 (Fed. Cir. Mar. 8, 2018) (non-precedential) (attached as Ex. D).

2. Summary Judgment

Rule 56(a) of the Federal Rules of Civil Procedure provides that a "court shall grant summary judgment if the movant shows that there is no genuine dispute as to any material fact and the movant is entitled to judgment as a matter of law." Fed. R. Civ. P. 56(a). The party opposing summary judgment must do more than prove "[t]he mere existence of a scintilla of evidence" to demonstrate the existence of a genuine issue of material fact. *Anderson v. Liberty Lobby, Inc*., 477 U.S. 242, 252 (1986). The opposing party must make a showing of specific facts—if the "evidence is merely colorable, or is not significantly probative, summary judgment may be granted." *Liberty Lobby*, 477 U.S. at 249-50 (citations omitted); *see, e.g., Oleksy v. GE*, No. 06 C 01245, 2013 U.S. Dist. LEXIS 89351, at *16-18 (N.D. Ill. June 26, 2013) (granting summary judgment and finding patents not invalid under § 101 as a matter of law).

B. The patents-in-suit are not directed to natural phenomena under step one of *Alice*.

1. Method of treatment claims are patent-eligible.

The asserted claims are not directed to an ineligible concept under step one of *Alice* because they recite methods of treating pain. The Supreme Court, the Federal Circuit, and the

USPTO have uniformly acknowledged that method of treatment claims are patent-eligible. First, the Supreme Court expressly limited its holding in *Mayo* by clarifying that the claims it invalidated under § 101 were "[u]nlike [] a typical patent on a new drug or a ***new way of using an existing drug***," which remain patent-eligible. *Mayo*, 132 S. Ct. at 1302 (emphasis added). The claims in *Mayo* recited a method of "***optimizing*** therapeutic efficacy," not a method of ***treating*** a disease. *Id.* at 1295 (emphasis added). The claimed methods involved measuring metabolites in the bloodstream to help calibrate the appropriate dosage of thiopurine drugs. Those claims "amounted to nothing more than observing or identifying the ineligible concept" (*CellzDirect*, 827 F.3d at 1048) because they did not require anyone to do anything with the data obtained via the claimed steps, apart from merely recognizing the law of nature itself (*i.e.*, "the relationship[] between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm"). *Mayo*, 132 S. Ct. at 1296.

> [T]he court construed the claim[s] . . . as not limited to instances in which the doctor actually decreases (or increases) the dosage level where the test results suggest that such an adjustment is advisable. . . [A] doctor using Mayo's test [thus] could violate the patent even if he did not actually alter his treatment decision in the light of the test. . . . [The claims] tell a treating doctor to measure metabolite levels and to consider the resulting measurements in light of the statistical relationships they describe. In doing so, they ***tie up the doctor's subsequent treatment decision whether that treatment does, or does not, change in light of the inference he has drawn using the correlations***.

Id. at 1296, 1302 (emphasis added). Second, the Federal Circuit held in *Rapid Lit. Mgt. Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042, 1049 (Fed. Cir. 2016), that "describing [a] process [as] the natural ability of the subject matter to undergo the process does not make the claim 'directed to' that natural ability." Otherwise, Courts "would find patent-ineligible methods of . . . treating cancer with chemotherapy (as directed to cancer cells' inability to survive chemotherapy), or treating headaches with aspirin (as directed to the human body's natural response to aspirin),"

which would contravene well-settled law. *Id.* Third, on May 5, 2016, the USPTO published patent eligibility guidance that analyzed the following fact pattern and hypothetical claims:

> Applicant has discovered that the presence of a protein known as "JUL-1" in a person's body is indicative that the person has julitis. . . . Prior to applicant's invention, and at the time the application was filed, julitis was conventionally treated with anti-tumor necrosis factor (TNF) antibodies. . . .
>
> 2. A method of diagnosing julitis in a patient, said method comprising:
>
> a. obtaining a plasma sample from a human patient;
>
> b. detecting whether JUL-1 is present in the plasma sample by contacting the plasma sample with an anti-JUL-1 antibody and detecting binding between JUL-1 and the antibody; and
>
> c. diagnosing the patient with julitis when the presence of JUL-1 in the plasma sample is detected. . . .
>
> 7. A method of treating a patient with julitis, the method comprising administering an effective amount of anti-TNF antibodies to a patient suffering from julitis.

Ex. E at 10-11. The USPTO found claim 2 ineligible because it recites "a mere data gathering step necessary to use the ['naturally occurring'] correlation." *Id.* at 11-12. By contrast, the USPTO found claim 7 patent-eligible because "[a]lthough the claim recites a nature-based product limitation (the anti-TNF antibodies), analysis of the claim as a whole indicates that the claim is focused on a process of practically applying the product to treat a particular disease (julitis), and not on the product *per se*." *Id.* at 15-16. The USPTO did not need to proceed to *Alice* step two, *i.e.*, the conventional nature of claim 7's method made no difference for purposes of § 101 because the claim was not directed to an ineligible concept. *Id.* Finally, following *CellzDirect*, on July 14, 2016, the USPTO issued another memorandum on patent eligibility. The USPTO found that *CellzDirect* accords with USPTO practice because it reaffirms the

eligibility of claims that "focus[] on a process for achieving [a] desired outcome . . . like ***thousands of other claims that recite . . . methods of treating disease***." Ex. F at 2 (emphasis added), citing *CellzDirect*, 827 F.3d at 1048-49.

Alvogen mischaracterized Pernix's claims as "nothing more than ***observations*** of how hydrocodone bitartrate is metabolized." D.I. 14 at 1 (emphasis added); *see also* D.I. 24 at 1. Alvogen ignored the language of the claims, which recite a method of treatment, not an observation. The inventors did observe an unexpected physiological response to a particular dosage unit as one step along their path towards the claimed inventions. But "that is not where they stopped, nor is it what they patented." *CellzDirect*, 827 F.3d at 1048. Rather, "as the first party with knowledge of" that response, they were "in an excellent position to claim applications of that knowledge." *Id.*, quoting *Myriad*, 133 S.Ct. at 2120 (quoting *Association for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303, 1349 (Fed. Cir. 2012) (Bryson, J., concurring in part and dissenting in part)). And "[t]hat is precisely what they did. They employed their . . . discovery to create a new and improved way" of ***treating pain*** in patients with hepatic impairment. *Id.* ("The end result of the '929 patent claims is not simply an observation or detection of the ability of hepatocytes to survive multiple freeze-thaw cycles. Rather, the claims are directed to . . . a '***method of producing*** a desired preparation of multi-cryopreserved hepatocytes.'") (citation omitted) (emphasis original).

As the foregoing case law and PTO guidance make clear, the focus must remain on the language of the claims, as different claims that "embody, use, reflect, rest upon, or apply" the same natural law can nevertheless lead to divergent conclusions under step one of *Alice*. *Mayo*, 132 S. Ct. at 1293. The claims here include the dispositive element that the Supreme Court found absent from the claims in *Mayo*, namely, a requirement to not only recognize but to

actually implement an unexpected observation. *See Molecular Pathology*, 689 F.3d at 1349 (Bryson, J., concurring in part and dissenting in part) ("[T]he discovery of [naturally-occurring gene] sequences is an unprotectable fact, just like Dr. King's discovery of the chromosomal location of the BRCA1 gene. Of course, Myriad is ***free to patent applications of its discovery***.") (emphasis added), *rev'd in part on other grounds*, *Myriad*, 133 S. Ct. at 2120. The asserted claims do not leave the treatment decision unresolved by merely requiring a doctor to "consider" a naturally-occurring correlation; the claims expressly require a "subsequent treatment decision," *i.e.*, no adjustment in the starting dose for patients with mild and moderate hepatic impairment relative to patients without hepatic impairment.[4] *Mayo*, 132 S. Ct. at 1302.[5]

2. The claims require administering a non-naturally occurring oral dosage unit.

Moreover, the asserted claims are directed to the administration of non-naturally-existing compositions, which independently renders the claims eligible under the first step of *Alice*. In *Molecular Pathology*, the Federal Circuit concluded that "claims to 'comparing' or 'analyzing' two gene sequences"—which occur in nature—"fall outside the scope of § 101 because they claim only abstract mental processes." *Id.* at 1334, *rev'd in part on other grounds*, *Myriad*, 133 S. Ct. at 2120. Yet the Court reached a different result for other claims even though they

[4] Claims 1-4 of the '760 patent explicitly recite that "the starting dose is not adjusted relative to a patient without hepatic impairment," while the remaining asserted claims require a PK profile that enables such dosing.

[5] Alvogen also tries to disparage the invention by speculating about the purported lack of difficulty in developing it. *See* D.I. 29 at 1 ("Pernix ***simply*** analyzed pharmacokinetic data from two patient populations . . . . That is ***merely*** the observation of a law of nature.") (emphasis added); D.I. 14 at 12-13 ("At best, the named inventors analyzed the pharmacokinetic data inhered to a formulation developed by others.") "But patent-eligibility does not turn on ease of execution or obviousness of application." *CellzDirect*, 827 F.3d at 1052 ("LTC's argument seems to be that, once it was discovered that hepatocytes could survive multiple freeze-thaw cycles, it would have been a simple task to repeat the known freeze-thaw process to arrive at the claimed invention. . . . Those are questions that are examined under separate provisions of the Patent Act.")

similarly recited an "abstract mental step of looking at two numbers and 'comparing' two host cells' growth rates." *Id.* at 1336. The Court held those claims eligible because, unlike the gene sequences, the host cells do ***not*** exist in nature but instead "arose from human effort":

> Claim 20 thus recites a screening method premised on the use of "transformed" host cells. Those cells . . . are not naturally occurring. Rather, they are derived by altering a cell to include a foreign gene, resulting in a man-made, transformed cell . . . . The transformed, man-made nature of the underlying subject matter in claim 20 makes the claim patent-eligible. The fact that the claim also includes the steps of determining the cells' growth rates and comparing growth rates does not change the fact that the claim is based on a man-made, non-naturally occurring transformed cell — patent-eligible subject matter.

Id. at 1336-37. Notably, the inclusion of man-made cells alone rendered the claimed process patent-eligible, irrespective of whether the steps of that process were known in the art. *Id.* at 1337 ("Whether such processes, including claim 20, meet other tests for patentability, such as novelty or nonobviousness, is not before us.")

The invention here uses hydrocodone, which is a semi-synthetic opioid, in the context of an oral dosage form, and neither the hydrocodone nor the dosage form exists in nature. Alvogen's expert Dr. Weinberger repeatedly admitted that at his deposition:

> Q. And this oral dosage form of hydrocodone doesn't appear in nature, right?
>
> A. That is my understanding, sir. That is correct.
>
> Q. It's not a natural phenomenon, right?
>
> A. I believe you are correct. . . .
>
> Q. Okay. And extended release formulations of hydrocodone do not appear in nature, right?
>
> A. I believe that is correct.
>
> Q. And they're not a natural phenomenon, right?
>
> A. That is correct. . . .
>
> Q. Okay. And the particular dose of hydrocodone extended-release tablet to use is not something that would appear in nature, right?
>
> A. These tablets do not appear in nature, no. . . .

> Q. Okay. So with regard to claim two, you would agree that administering an oral dose of hydrocodone is -- the hydrocodone is made by a person and is not something that appears in nature?
>
> A. Yes, sir.
>
> Q. And then claim one, and therefore claim two, says that the oral unit dosage of hydrocodone is an extended-release formulation. And so you would agree that the extended-release formulation that's recited in claim two does not appear in nature and is not a natural phenomena, right?
>
> A. I think what we agreed was that the hydrocodone, which is in claim one and then in claim two, is not a natural product or appears in nature
>
> Q. Okay. So the extended-release form of a hydrocodone product is not a natural product and is not a natural phenomenon as well as recited in claim two?
>
> A. Yes, sir.

Ex. G at 10:25-11:12, 12:4-13, 13:7-12, 25:7-26:5 (objections omitted). Thus, the claims are not directed to a natural phenomenon because they require administering a man-made dosage unit that contains a non-naturally-occurring opioid.

C. The claims recite an inventive concept under step two of *Alice*.

Even if the patents-in-suit claim a natural phenomenon (which they do not), they are still directed to patent-eligible subject matter because the claims recite an inventive concept. In *Mayo*, the Court interpreted the claims as "tell[ing] doctors to engage in well-understood, routine, conventional activity previously engaged in by scientists who work in the field," and found such "[p]urely conventional or obvious" activity "[in]sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law." *Mayo*, 132 S. Ct. at 1298. By contrast, the claims here recite unconventional steps, namely, administering a single entity extended release hydrocodone oral dosage unit to patients with mild and moderate hepatic impairment without adjusting the starting dose relative to patients without hepatic impairment (or a PK profile that enables such dosing). Commercial prior art extended release opioids required dosage adjustments for hepatically impaired patients. *See* Section III, *supra*. Thus, unlike the

claims in *Mayo*, the claims here do not merely "append[] conventional steps" (*id.* at 1300) to a law of nature.

The Court's *Markman* decision forecloses any argument to the contrary. Alvogen asserted in its motion to dismiss under § 101 that "the 'wherein' clauses in the '760 patent add nothing to confer patentability" and therefore could not amount to an inventive concept. D.I. 14 at 11. Alvogen reiterated that argument in its claim construction briefs. D.I. 59 at 14 (arguing the wherein clauses "add[] nothing to the patentability or substance of the claim") (citation omitted). Alvogen contended in particular that "the phrase[,] '[wherein the] starting dose is not adjusted relative to a patient without hepatic impairment[,]' . . . is a statement of purpose and result, and not something that produced any 'manipulative difference' in the steps of the claims." *Id.*, quoting, *inter alia*, *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) ("*BMS*"). According to Alvogen, that phrase therefore "is not a limitation because it simply states an intended outcome which is nothing more than the result of a purely mental step (*i.e.*, a doctor mentally comparing an unspecified 'starting' hydrocodone dose for an impaired patient to an unspecified starting hydrocodone dose that would have been used for an unspecified patient who is unimpaired.") *Id.* at 13, citing *BMS*, 246 F.3d at 1376.

In *BMS*, the Court construed the term, "[a] method for treating a cancer patient to effect regression of a taxol sensitive tumor, said method being associated with reduced hematologic toxicity," as a non-limiting "statement of purpose and intended result" that "do[es] not impart patentability to Bristol's claims." *Id.* at 1376-77. The Court did so because the phrase "does not result in a manipulative difference in the steps of the claim," which "are performed in the same way regardless whether or not the patient experiences" the intended result. *Id.* at 1375-76. The Court also emphasized that the term does "not distinguish th[e] claims over the prior art." *Id.* at

1375-77 (accepting defendants' argument that "Bristol's sole contribution was in recognizing a new result of that same use, *i.e.*, that it worked to treat cancer": "the claimed process here is not directed to a new use; it is the same use, and it consists of the same steps as described by [prior art]."). Thus, in analyzing whether the term limited the claims, the Court compared the claimed process with conventional processes, and looked for an identity of physical steps—just as the Court did in *Mayo* when analyzing the claims under step two of (what later became) the *Alice* framework. *See, e.g.*, *CellzDirect*, 827 F.3d at 1051 (noting that the physical steps in *Mayo* "were already being performed by those in the field; adding knowledge of the natural law was insufficient to render the claims patent eligible"); *Genetic Techs. Ltd. v. Merial LLC*, 818 F.3d 1369, 1377 (Fed. Cir. 2016) (looking at "the physical steps by which claim 1 implements the natural law of linkage disequilibrium between coding and non-coding regions to determine whether they provide more than 'well-understood, routine, conventional activity' already engaged in by those in the field"), quoting *Mayo*, 132 S.Ct. at 1294; *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371, 1377-78 (Fed. Cir. 2015) (preparing, amplifying, and detecting genetic sequences were already being done; performing those same steps on a newly discovered, naturally-occurring substrate did not amount to an inventive concept).

In its *Markman* decision, this Court rejected Alvogen's argument that the starting dose term does not limit the claims. It performed the same analysis that the Federal Circuit performed in *BMS*—with the opposite outcome:

> [not] adjusting the starting dose relative to a patient without hepatic impairment is, in fact, a **manipulative difference over the prior art** . . . .
>
> the ability of a patient with a hepatic impairment to gain the same benefits from the opioid that a non-hepatically impaired patient receives in just one dose **differs from the prior art**. . . .

> the claim phrase explaining that hepatically and non-hepatically impaired patients get the same starting dose . . . does have an effect on how the administering step is performed . . . because patients with hepatic impairment ingest a **different dose than they normally would, given the prior art**;
>
> a physician would ***not*** normally give a hepatically impaired patient the same dose as a patient without a hepatic impairment; and
>
> [s]ince the method of treating pain in the hepatically impaired patient is **different than the prior art's method** of treating pain in that same patient, having a patient ingest the same initial dose regardless of their hepatic impairment is not just a mental step.

D.I. 69 at 3 n.2 (italicized emphasis original; underlined emphasis added). The Court's *Markman* findings therefore establish that the claims recite unconventional steps and satisfy step two of *Alice*. *See CellzDirect*, 827 F.3d at 1051 ("Repeating a step that the art taught should be performed only once can hardly be considered routine or conventional. This is true even though it was the inventor's discovery of something natural that led them to do so."). And those fact findings are not open for re-litigation. *Bondyopadhyay v. United States*, No. 14-147C, 2018 U.S. Claims LEXIS 79, at *14-15 (Fed. Cl. Feb. 9, 2018) ("[P]rior findings and the claim construction based on those findings are law of the case and 'are not available for redetermination'"), *quoting Del Mar Avionics, Inc. v. Quinton Instrument Co.*, 836 F.2d 1320, 1324 (Fed. Cir. 1986); *Anderson Corp v. Fiber Composites, LLC*, 474 F.3d 1361, 1371 n.2 (Fed. Cir. 2007) (recognizing district court's claim construction as law of the case for purposes of trial); *see also, e.g.*, *Sprint Communs. Co. L.P. v. Cox Communs. Inc.*, No. 12-487-JFB, 2017 U.S. Dist. LEXIS 186266, at *43-45 (D. Del. Nov. 9, 2017) (refusing to allow party to advance arguments "contrary to the Court's claim construction" ruling), citing *Liquid Dynamics Corp. v. Vaughan Co.*, 449 F.3d 1209, 1224 n.2 (Fed. Cir. 2006); *Gemtron Corp. v. Saint-Gobain Corp.*, No. 1:04-0387, 2008 U.S. Dist. LEXIS 32646, at *7-8 (W.D. Mich. Apr. 21, 2008) (rejecting an argument that merely "recycles . . . rejected claim construction arguments"), *aff'd, Gemtron Corp. v. Saint-*

Gobain Corp., 572 F.3d 1371 (Fed. Cir. 2009). Thus, Alvogen can no longer argue, as it did in its motion to dismiss, that the starting dose limitation does not impart patentability, or that the remaining limitations "implicitly tell a doctor to treat pain with hydrocodone according to well-known and art-recognized methods." D.I. 29 at 5; *HSM Portfolio LLC v. Elpida Memory, Inc.*, 160 F. Supp. 3d 708, 717 (D. Del. 2016) (granting summary judgment because a theory that is "inconsistent with the Court's claim construction order . . . fails to create a genuine dispute").

Alvogen also argued in its motion to dismiss under § 101 that "[t]he 'administering' steps in the '760 patent, like the 'administering' step in *Mayo* . . . simply refers to the relevant audience, namely doctors who treat patients with certain diseases [and having mild or moderate hepatic impairment] with [hydrocodone] drugs." D.I. 14 at 11 (citation omitted). Alvogen subsequently flip-flopped during claim construction, arguing that "administering" refers neither to doctors nor to any other "relevant audience," but rather to a ***physical act*** performed by a ***patient.*** Alvogen argued in particular that "administering" "can only be read to mean dispensing into the body of the patient." D.I. 64 at 2.

> In the context of the asserted patents, the meaning of "administering" is the direct action of putting medicine into the body—not the indirect action of supervising or managing the use of the medicine by "prescribing" or "dispensing" it. . . . [T]he "patents consistently refer to the term 'administering' ***solely to describe the physical act of delivering the drug into or onto the body*** . . . . "

Id. at 4; D.I. 59 at 5-7 (emphasis added) (citation omitted). The Court accepted Alvogen's latter argument and construed "administering" to require "delivering into the body." D.I. 69 at 1. In doing so, the Court expressly rejected an interpretation of administering that would have encompassed the physician's act of "prescribing" or "dispensing." *Id.* at 2 n.1. Thus, unlike in *Mayo*, here "administering" does not merely "inform" a doctor of a natural law, but rather requires "practically applying a product to treat a particular" condition (pain) in an

unconventional way. Ex. E at 16. And, having persuaded the Court to adopt that meaning during claim construction, Alvogen cannot now revert back to the contrary meaning it urged in its motion to dismiss. *HSM*, 160 F. Supp. 3d at 717 (disregarding conclusion that "contravenes previous representations made . . . to this Court.").

Accordingly, no material facts remain in dispute, and the asserted claims satisfy step two of *Alice* as a matter of law.

D. The claims do not raise preemption concerns.

Finally, "while pre-emption is not the test for determining patent-eligibility," it remains the "concern that undergirds . . . § 101 jurisprudence." *CellzDirect*, 827 F.3d at 1052; *Alice*, 134 S.Ct. at 2358. The claims here do not preempt all uses of hydrocodone, all uses of hydrocodone oral dosage units, all uses of extended release hydrocodone oral dosage units, all uses of extended release hydrocodone oral dosage units to treat pain, or even all uses of extended release hydrocodone oral dosage units to treat pain in patients with mild or moderate hepatic impairment. The extended release hydrocodone oral dosage unit disclosed in the Bond abstract, for example, does not infringe the claims; it does not meet the claimed PK profile and requires an adjusted starting dose for patients with mild and moderate hepatic impairment.[6] The Bond formulation further confirms that the claims are not directed to any natural phenomena concerning hydrocodone metabolism, as it demonstrates that the claimed PK profile (and consequent elimination of the need to adjust the starting dose) results only from the

[6] The Bond formulation was approved in 2017 as Vantrela™ ER, and the Vantrela™ ER label states: "In patients with mild or moderate hepatic impairment, ***initiate therapy with one half of the recommended initial dose*** followed by careful dose titration. Use of alternate analgesics is recommended for patients who require a VANTRELA ER dose of less than 15 mg." Ex. B at 1 (emphasis added).

administration of particular formulations, and not from a patent-ineligible universal law of nature like, *e.g.*, gravity. *Diamond v. Chakrabarty*, 447 U.S. 303, 309 (1980).

V. Conclusion

The Court should grant Pernix's motion and find that the patents-in-suit are directed to eligible subject matter under § 101.

Respectfully submitted,

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